

METHOD AND APPARATUS FOR AUTOMATING A MATRIX-ASSISTED
LASER DESORPTION/IONIZATION (MALDI) MASS SPECTROMETER

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser.
No. 09/507,423, filed February 18, 2000.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to mass spectrometry and the analysis of chemical samples, and more particularly to the apparatuses and methods for the automated preparation and introduction of samples into a matrix-assisted laser desorption/ionization (MALDI) mass spectrometer. Described herein is a system utilizing a multiple part capillary device with a robot for use in mass spectrometry (particularly with ionization sources) to transport ions to the mass spectrometer for analysis therein.

BACKGROUND OF THE PRESENT INVENTION

The present invention relates to a means of delivering ions to a mass spectrometer. Mass spectrometry is an important tool in the analysis of a wide range of chemical compounds. Specifically, mass spectrometers can be used to determine the molecular weight of sample compounds. The analysis of samples by mass spectrometry consists of three main steps -- formation of ions from sample

1 material, mass analysis of the ions to separate the ions from one
2 another according to ion mass, and detection of the ions. A
3 variety of means exist in the field of mass spectrometry to perform
4 each of these three functions. The particular combination of means
5 used in a given spectrometer determine the characteristics of that
6 spectrometer.

7 To mass analyze ions, for example, one might use a magnetic
8 (B) or electrostatic (E) analyzer. Ions passing through a magnetic
9 or electrostatic field will follow a curved path. In a magnetic
10 field the curvature of the path will be indicative of the momentum-
11 to-charge ratio of the ion. In an electrostatic field, the
12 curvature of the path will be indicative of the energy-to-charge
13 ratio of the ion. If magnetic and electrostatic analyzers are used
14 consecutively, then both the momentum-to-charge and energy-to-
15 charge ratios of the ions will be known and the mass of the ion
16 will thereby be determined. Other mass analyzers are the
17 quadrupole (Q), the ion cyclotron resonance (ICR), the time-of-
18 flight (TOF), and the quadrupole ion trap analyzers.

19 Before mass analysis can begin, however, gas phase ions must
20 be formed from sample material. If the sample material is
21 sufficiently volatile, ions may be formed by electron ionization
22 (EI) or chemical ionization (CI) of the gas phase sample molecules.
23 For solid samples (e.g. semiconductors, or crystallized

1 materials), ions can be formed by desorption and ionization of
2 sample molecules by bombardment with high energy particles.
3 Secondary ion mass spectrometry (SIMS), for example, uses keV ions
4 to desorb and ionize sample material. In the SIMS process a large
5 amount of energy is deposited in the analyte molecules. As a
6 result, fragile molecules will be fragmented. This fragmentation
7 is undesirable in that information regarding the original
8 composition of the sample -- e.g., the molecular weight of sample
9 molecules -- will be impossible to determine.

10 For more labile, fragile molecules, other ionization methods
11 now exist. The plasma desorption (PD) technique was introduced by
12 Macfarlane et al. in 1974 (Macfarlane, R. D.; Skowronski, R. P.;
13 Torgerson, D. F., *Biochem. Biophys. Res Commun.* 60 (1974) 616).
14 Macfarlane et al. discovered that the impact of high energy (MeV)
15 ions on a surface, like SIMS would cause desorption and ionization
16 of small analyte molecules, however, unlike SIMS, the PD process
17 also results in the desorption of larger, more labile species --
18 e.g., insulin and other protein molecules.

19 Lasers have been used in a similar manner to induce desorption
20 of biological or other labile molecules. See, for example,
21 VanBreeman, R.B.; Snow, M.; Cotter, R.J., *Int. J. Mass Spectrom.*
22 *Ion Phys.* 49 (1983) 35; Tabet, J.C.; Cotter, R.J., *Anal. Chem.* 56
23 (1984) 1662; or Olthoff, J.K.; Lys, I.; Demirev, P.; Cotter, R.

1 J., *Anal. Instrument.* 16 (1987) 93. Cotter et al. modified a CVC
2 2000 TOF mass spectrometer for infrared laser desorption of
3 involatile biomolecules, using a Tachisto (Needham, Mass.) model
4 215G pulsed carbon dioxide laser. The plasma or laser desorption
5 and ionization of labile molecules relies on the deposition of
6 little or no energy in the analyte molecules of interest. The use
7 of lasers to desorb and ionize labile molecules intact was enhanced
8 by the introduction of matrix assisted laser desorption ionization
9 (MALDI) (Tanaka, K.; Waki, H.; Ido, Y.; Akita, S.; Yoshida, Y.;
10 Yoshida, T., *Rapid Commun. Mass Spectrom.* 2 (1988) 151 and Karas,
11 M.; Hillenkamp, F., *Anal. Chem.* 60 (1988) 2299). In the MALDI
12 process, an analyte is dissolved in a solid, organic matrix. Laser
13 light having a wavelength that is absorbed by the solid matrix but
14 not by the analyte is used to excite the sample. Thus, the matrix
15 is excited directly by the laser, and the excited matrix sublimates
16 into the gas phase carrying with it the analyte molecules. The
17 analyte molecules are then ionized by proton, electron, or cation
18 transfer from the matrix molecules to the analyte molecules. This
19 process, MALDI, is typically used in conjunction with time-of-
20 flight mass spectrometry (TOFMS) and can be used to measure the
21 molecular weights of proteins in excess of 100,000 daltons.

22 Recently, MALDI has been especially gaining acceptance as a
23 way to ionize large molecules such as proteins. MALDI requires

1 that samples applied to the surface of a sample support must be
2 introduced into the vacuum system of the mass spectrometer.
3 According to the prior art, a relatively large number of sample are
4 introduced together on a support, and the sample support is moved
5 within the vacuum system in such a way that the required sample is
6 situated specifically in the focus of the laser's lens system. The
7 analyte samples are placed on a sample support in the form of small
8 drops of a solution, which dry very quickly and leave a sample spot
9 suitable for MALDI. Normally a matrix substance is added to the
10 solution for the MALDI process and the sample substances are
11 encased in the crystals when the matrix substance crystallizes
12 while drying. There are other methods known in the prior art, such
13 as the application of sample substances to an already applied and
14 dried matrix layer.

15 Current methods use visual control of the sample spots via
16 microscopic observation. Thus, these are not truly automated.
17 True automation opens up the possibility of processing large
18 numbers of samples. It is well established within the art that
19 microtiter plates are used for parallel processing of many samples.
20 The body size of these plates is 80 by 125 millimeters, with a
21 usable surface of 72 by 108 millimeters. There are commercially
22 available sample processing systems which work with microtiter
23 plates of this size. These originally contained 96 small

1 exchangeable reaction vials in a 9mm grid on a usable surface of 72
2 by 108 millimeters. Today, plates of the same size with 384
3 reaction wells imbedded solidly in plastic in a 4.5 mm grid have
4 become standard.

5 The use of Atmospheric pressure ionization (API) is also well
6 known in the prior art. Typically, analyte ions are produced from
7 liquid solution at atmospheric pressure. One of the more widely
8 used methods, known as electrospray ionization (ESI), was first
9 suggested by Dole et al. (M. Dole, L.L. Mack, R.L. Hines, R.C.
10 Mobley, L.D. Ferguson, M.B. Alice, *J. Chem. Phys.* 49, 2240, 1968).
11 In the electrospray technique, analyte is dissolved in a liquid
12 solution and sprayed from a needle. The spray is induced by the
13 application of a potential difference between the needle (where the
14 liquid emerges) and a counter electrode. By subjecting the sample
15 liquid to a strong electric field, it becomes charged, and as a
16 result, it "breaks up" into smaller particles if the charge imposed
17 on the liquid's surface is strong enough to overcome the surface
18 tension of the liquid (i.e., as the particles attempt to disperse
19 the charge and return to a lower energy state). This results in
20 the formation of finely charged droplets of solution containing
21 analyte molecules. These droplets further evaporate leaving behind
22 bare charged analyte ions.

23 Electrospray mass spectrometry (ESMS) was introduced by

1 Yamashita and Fein (M. Yamashita and M.B. Fein, *J. Phys. Chem.* 88,
2 4671, 1984). To establish this combination of ESI and MS, ions had
3 to be formed at atmospheric pressure, then introduced into the
4 vacuum system of a mass analyzer via a differentially pumped
5 interface. The combination of ESI and MS affords scientists the
6 opportunity to mass analyze a wide range of samples, and ESMS is
7 now widely used primarily in the analysis of biomolecules (e.g.
8 proteins) and complex organic molecules.

9 In the intervening years a number of means and methods useful
10 to ESMS and API-MS have been developed. Specifically, a great deal
11 of work has focused on sprayers and ionization chambers. In
12 addition to the original electrospray technique, pneumatic assisted
13 electrospray, dual electrospray, and nano electrospray are now also
14 widely available. Pneumatic assisted electrospray (A.P. Bruins,
15 T.R. Covey, and J.D. Henion, *Anal. Chem.* 59, 2642, 1987) uses
16 nebulizing gas flowing past the tip of the spray needle to assist
17 in the formation of droplets. The nebulization gas assists in the
18 formation of the spray and thereby makes the operation of ESI
19 easier. Nano electrospray (M.S. Wilm, M. Mann, *Int. J. Mass*
20 *Spectrom. Ion Processes* 136, 167, 1994) employs a much smaller
21 diameter needle than the original electrospray. As a result the
22 flow rate of sample to the tip is lower and the droplets in the
23 spray are finer. However, the ion signal provided by nano

1 electrospray in conjunction with MS is essentially the same as with
2 the original electrospray. Nano electrospray is therefore much
3 more sensitive with respect to the amount of material necessary to
4 perform a given analysis.

5 Sample preparation robots (e.g. Gilson) have been used in the
6 prior art for the automated injection of sample aliquots into an
7 ESI source. In such a case, solution is pumped continuously from
8 a resevoir to the sprayer of an ESI source. Sampe aliquots are
9 injected into this solution stream and are thereby carried through
10 a transfer line to the sprayer.

11 Many other ion production methods might be used at atmospheric
12 or elevated pressure. For example, MALDI has recently been adapted
13 by Victor Laiko and Alma Burlingame to work at atmospheric pressure
14 (Atmospheric Pressure Matrix Assisted Laser Desorption Ionization,
15 poster #1121, 4th International Symposium on Mass Spectrometry in
16 the Health and Life Sciences, San Francisco, Aug. 25 - 29, 1998)
17 and by Standing et al. at elevated pressures (Time of Flight Mass
18 Spectrometry of Biomolecules with Orthogonal Injection +
19 Collisional Cooling, poster #1272, 4th International Symposium on
20 Mass Spectrometry in the Health and Life Sciences, San Francisco,
21 Aug. 25 - 29, 1998; and Orthogonal Injection TOFMS *Anal. Chem.*
22 71(13), 452A (1999)). The benefit of adapting ion sources in this
23 manner is that the ion optics and mass spectral results are largely

1 independent of the ion production method used.

2 An elevated pressure ion source always has an ion production
3 region (where ions are produced) and an ion transfer region (where
4 ions are transferred through differential pumping stages and into
5 the mass analyzer). The ion production region is at an elevated
6 pressure -- most often atmospheric pressure -- with respect to the
7 analyzer.

8 In much of the prior art the ion production region will often
9 include an ionization "chamber". In an ESI source, for example,
10 liquid samples are "sprayed" into the "chamber" to form ions. The
11 design of the ionization chamber used in conjunction with API-MS
12 has had a significant impact on the availability and use of these
13 ionization methods with MS. Prior art ionization chambers are
14 inflexible in that a given ionization chamber can be used readily
15 with only a single ionization method and a fixed configuration of
16 sprayers. For example, in order to change from a simple
17 electrospray method to a nano electrospray method of ionization,
18 one had to remove the electrospray ionization chamber from the
19 source and replace it with a nano electrospray chamber (see also,
20 Gourley et al. United States Pat. No. 5,753,910, entitled Angled
21 Chamber Seal for Atmospheric Pressure Ionization Mass
22 Spectrometry). In a co-pending application entitled Ionization
23 Chamber For Atmospheric Pressure Ionization, this problem is

1 addressed by disclosing an API ionization chamber providing
2 multiple ports for employing multiple devices in a variety of
3 combinations (e.g., any type of sprayer, lamp, microscope, camera
4 or other such device in various combinations). Further, any given
5 sprayer may produce ions in a manner that is synchronous or
6 asynchronous with the spray from any or all of the other sprayers.
7 By spraying in an asynchronous manner, analyte from a multitude of
8 inlets may be sampled in a multiplexed manner.

9 Analyte ions produced via an API method need to be transported
10 from the ionization region through regions of differing pressures
11 and ultimately to a mass analyzer for subsequent analysis (e.g.,
12 via TOFMS, Fourier transform mass spectrometry (FTMS), etc.). In
13 prior art sources, this was accomplished through use of a small
14 orifice or capillary tube between the ionization region and the
15 vacuum region. An example of such a prior art capillary tube is
16 shown in FIG. 1. As depicted, capillary 7 comprises a generally
17 cylindrical glass tube 2 having an internal bore 4. The ends of
18 capillary 7 include a metal coating (e.g., platinum, copper, etc.)
19 to form conductors 5 which encompass the outer surface of capillary
20 7 at its ends, leaving a central aperture 6 such that the entrance
21 and exit to internal bore 3 are left uncovered. Conductors 5 may
22 be connected to electrical contacts (not shown) in order to
23 maintain a desired space potential at each end of capillary 7. In

1 operation, a first electrode (one of conductors 5) of capillary 7
2 may be maintained at an extreme negative potential (e.g., -4,500V),
3 while the other electrode (the other of conductors 5), which may
4 form the first stage of a multi-stage lensing system for the final
5 direction of the ions to the spectrometer, may be maintained at a
6 positive potential (e.g., 160 volts).

7 It is often observed that the capillaries used in MS analysis
8 acquire deposits over time. Therefore, through normal operation
9 the capillaries need to be regularly cleaned or even replaced. To
10 do so, the MS system must be turned off before the capillary can be
11 removed -- requiring the pumps to be shut down and the vacuum
12 system to be broken -- thereby rendering the system unavailable for
13 hours and even days at a time.

14 More recently, Lee et al. U.S. Pat. No. 5,965,883 attempted to
15 solve this problem in the manner shown by FIG. 2. Shown in FIG. 2
16 is capillary 8 which comprises an outer capillary sleeve 9
17 surrounding an inner capillary tube 10. Sleeve 9 has substantially
18 cylindrical inner surface 11 and outer surface 14. Similarly, tube
19 10 has substantially cylindrical inner surface 12 and outer surface
20 13. The innermost channel, or bore, of capillary 8 is
21 substantially formed by inner surface 12 of tube 10. Capillary 8
22 is substantially radially symmetrical about its central
23 longitudinal axis 15 extending from an upstream end 16 to a

1 downstream end 17. At each end, capillary 8 has conductive end
2 caps 18 comprising the unitary combination of a tubular body having
3 cylindrical inner surface 20 and outer surface 21 and an end plate
4 22 having inner surface 23 and outer surface 24 with a central
5 aperture. The tubular body of end cap 18 encompasses and is in
6 circumferential engagement with a reduced diameter portion 25 of
7 sleeve 9 adjacent to the respective ends of capillary 8, such that
8 the external diameter of end cap 18 is substantially the same as
9 the external diameter of sleeve outer surface 14.

10 In order to remove tube 10, end cap 18 at the upstream end of
11 capillary 8 is first removed. A removal tool (not shown) is
12 inserted into the tube as to engage the tube's inner surface 12.
13 It is further suggested by the prior art that in order to remove
14 tube 10 it may be necessary to apply a slight torque orthogonal to
15 axis 15, or other appropriate means such as bonding a removal tool
16 to the tube using an adhesive. Once the tube is withdrawn, a
17 replacement tube may be inserted into sleeve 9. However, this too
18 is difficult and cumbersome, requiring tools to remove and replace
19 the inner capillary tube.

20 Such prior art designs for the transfer capillary have
21 inherent limitations relating to geometry, orientation, and ease of
22 use. The capillary according to these prior art designs is
23 substantially fixed in the source. Only if the instrument -- or at

1 least the source -- is vented to atmospheric pressure can the
2 capillary be removed. The geometric relation of the capillary is
3 therefore fixed with respect to the source and all its components.
4 This implies that the ion production means - e.g. an electrospray
5 needle, atmospheric pressure chemical ionization sprayer, or MALDI
6 probe - must be positioned with respect to the capillary entrance.
7 In order to change from one ion production means to another - e.g.
8 from an electrospray needle to a nano electrospray needle - the
9 first means must be removed from the vicinity of the capillary
10 entrance and the second must then be properly positioned with
11 respect to the capillary entrance. For any production means, there
12 will be an optimum geometry between the means and the capillary
13 entrance at which the ion current passing into the analyzer is
14 maximized. To achieve this optimum, a positioning means must be
15 provided for positioning the ion production means with respect to
16 the capillary entrance. This might take the form of precision
17 machined components, a translation stage on which the ion
18 production means is mounted, or some other device. If the ion
19 production means is required or desired to be remote from the
20 source, a long, fixed length capillary would have to be produced
21 and installed (in a fixed position) in the source.

22 Another limitation of prior art capillaries relates to the
23 orientation of the capillary bore with respect to the ion

1 production means. Such orientation can be important for the
2 operation of the source. One major consideration in the operation
3 of an electrospray source is the formation of large droplets from
4 the analyte solution at the spray needle. Such droplets do not
5 readily evaporate. If these droplets enter the capillary, they may
6 cause the capillary to become contaminated with a residue of
7 analyte molecules and salts. In view of this, Apfel et al. in US
8 patents 5,495,108 and 5,750,988 describe apparatuses for API
9 sources wherein the axis of the bore of the capillary 110 is at an
10 angle of 90° with respect the axis of the bore of the spray needle
11 111, as depicted in FIG. 3. According to Apfel et al., certain
12 experimental conditions lead to the production of large droplets by
13 the spray needle. These large droplets will move away from the
14 spray needle along the axis of the sprayer. However, an electric
15 field between the spray needle and the capillary will cause ions
16 formed from the spray to move towards the capillary. In this way,
17 the ions are separated from the spray droplets and the droplets do
18 not enter the capillary. However, this orientation is fixed in the
19 prior art source of Apfel. To change this orientation, one would
20 have to move the spray needle.

21 Prior art capillaries are further limited in the geometry of
22 the capillary bore. That is, prior art capillaries, as depicted in
23 FIGS. 1-3, are substantially straight (i.e., cylindrically

1 symmetric) and fixed (i.e., the geometry of the capillary and its
2 bore is fixed at the time of manufacture). However, as described
3 in the co-pending application METHOD AND APPARATUS FOR A MULTIPLE
4 PART CAPILLARY DEVICE FOR USE IN MASS SPECTROMETRY Serial No.
5 09/507,423 a capillary which can be cleaned or replaced without
6 the need to shut down the entire mass spectrometer in which it
7 resides now exists. The use of this capillary within the system
8 described herein allows ionization to occur within the MALDI tray
9 as opposed to occurring within the vacuum.

10 Others have disclosed atmospheric pressure matrix-assisted
11 laser desorption/ionization (AP-MALDI). Laiko et al. disclose an
12 AP-MALDI apparatus for the transfer of ions from an atmospheric
13 pressure ionization region to a high vacuum region, which is
14 pneumatically assisted (PA) by a stream of nitrogen gas. (Victor V.
15 Laiko, Michael A. Baldwin and Alma L. Burlingame, "Atmospheric
16 Pressure Matrix-Assisted Laser Desorption/Ionization Mass
17 Spectrometry", Analytical Chemistry, Vol. 72, No. 4, February 4,
18 2000). The invention of matrix-assisted laser
19 desorption/ionization (MALDI) and electrospray ionization (ESI) are
20 considered the most powerful tools for detection, identification,
21 and characterization of biopolymers such as peptides, proteins, and
22 DNA. MALDI and ESI enable the production of intact heavy molecular
23 ions from a condensed phase, where MALDI is for solids and ESI is

1 for liquids. Although, MALDI's target material density drops
2 rapidly after laser desorption, from a high value characteristic of
3 the initial solid phase to a very low value. Hence, a new
4 ionization source combines atmospheric pressure and MALDI, which
5 was called atmospheric pressure (AP) MALDI. AP-MALDI produces a
6 uniform ion cloud under atmospheric pressure conditions. The
7 apparatus disclosed in Laiko, i.e., for PA-AP-MALDI, is readily
8 interchangeable with electrospray ionization on an orthogonal
9 acceleration TOF mass spectrometer. According to Laiko, PA-AP-
10 MALDI can detect low femtomole amounts of peptides in mixtures with
11 good signal-to-noise ratio and with less discrimination for the
12 detection of individual peptides in a protein digest. Thus, total
13 sample consumption is higher for PA-AP-MALDI than vacuum MALDI, as
14 the transfer of ions into the vacuum system is relatively
15 inefficient.

16 Yet another high throughput MALDI elevated pressure mass
17 spectrometry technique and apparatus is disclosed by Schevchenko et
18 al. ("MALDI Quadrupole Time-of-Flight Mass Spectrometry: A Powerful
19 Tool for Proteomic Research", Analytical Chemistry, Vol. 72, No. 9,
20 May 1, 2000). More particularly, Shevchenko et al. disclose use of
21 a MALDI QqTOF mass spectrometer to achieve high mass resolution and
22 accuracy in the identification of proteins. The apparatus
23 disclosed by Schevchenko includes interfacing an orthogonal

1 injection TOF MS to a hybrid quadrupole TOF MS (QqTOF) to form a
2 MALDI QqTOF instrument, whereby a collisional damping interface
3 cools the ions before they enter the analytical quadrupole Q.
4 According to Schevchenko, once the ions are cooled, they can be
5 transported through the quadrupoles more efficiently for
6 measurement of the whole mass spectrum. A precursor ion can be
7 selected in the quadrupole Q and fragmented in the collision cell
8 q. Measurement of the product ions in the TOF section then
9 provides a MS/MS spectrum of the selected precursor, thus carrying
10 out both peptide mass mapping and MS/MS measurement on the same
11 target in the same experiment. This process provides a high mass
12 selection of precursor ions, precise tuning of the collision
13 energy, and a much simplified calibration procedure. Also,
14 Schevchenko et al. suggest that such an analytical approach lends
15 itself to automation in obtaining MALDI spectra. However,
16 Schevchenko et al. are silent as to how this might be achieved.

17 Also, Franzen et al. U.S. Patent No. 5,663,561 (Franzen)
18 teaches a device and method for the desorption and ionization of
19 labile substance molecules at atmospheric pressure by MALD followed
20 by chemical ionization (APCI). The method of Franzen consists of
21 desorbing the analyte substances, which are mixed with decomposable
22 substances (matrix substances) in solid form on a solid support, by
23 laser irradiation at atmospheric pressure into a gas stream, and to

1 add sufficient ions for proton transfer reactions to the gas
2 stream. The objective of the method and apparatus of Franzen et
3 al. is to transfer large molecules on solid sample support from
4 solid state to a state of ionized gas phase molecules to be
5 subjected to mass spectrometric analysis in an efficient manner.

6 The system disclosed in Franzen et al. generates ions from
7 macromolecular substances in an area outside the vacuum, instead of
8 within the vacuum, and separates the ionization process from the
9 desorption process. Since new development of ion transfer from
10 atmospheric pressure have become possible, external ionization has
11 become effective and relatively economical. Thus, Franzen et al.
12 recognized the problem of evaporating the non-volatile analyte
13 substances into the surrounding gas. Therefore, the method and
14 apparatus of Franzen et al. support the desorption process by
15 photolytic and thermolytic processes triggered by laser photons.
16 Consequently, the matrix material would decompose explosion-like
17 into small gas molecules which can blast the analyte molecules into
18 the surrounding gas. Then, the matrix molecules in the photolytic
19 and thermolytic processes are broken down into smaller molecules.
20 According to Franzen et al., if a matrix substance is selected in
21 such a way that the product of its decomposition is gaseous in its
22 normal state, the large, embedded analyte molecules would be
23 catapulted into the gas phase. Of course, the matrix material then
24 has to be selected such that the transfer of heat to the analyte
25 molecules is minimal.

1 Moreover, in each of these systems, the samples are positioned
2 outside of the vacuum system of the mass spectrometer for
3 ionization (e.g., a MALDI target, sample plate, etc.). The present
4 invention recognizes this and provides a simple and efficient
5 method and apparatus for ionizing samples and introducing the
6 sample ions into a mass spectrometer with the sample positioned
7 outside of the vacuum system of the mass spectrometer.

8 Also, it has been recognized that a need exists for a simple,
9 fast, efficient and reliable means of integrating a robot with
10 various ionization sources for automating the preparation and
11 introduction of samples into a mass spectrometer, and more
12 particularly into an atmospheric pressure MALDI mass spectrometer.
13 The present invention provides a novel solution to this problem.
14

15 SUMMARY OF THE INVENTION

16 The present invention relates generally to mass spectrometry
17 and the analysis of chemical samples, and more particularly to the
18 robotic interface of sample introduction into a source region of a
19 mass spectrometer using specially designed multiple part capillary
20 tubes.

21 It is a first object of the invention to provide an improved
22 method and apparatus for the automatic preparation and introduction
23 of samples into a mass spectrometer for subsequent mass analysis.

24 It is another object of the invention to provide a method and
25 apparatus for the automatic preparation and introduction of samples

1 maintained at atmospheric pressure (i.e., outside the vacuum
2 system) into a mass spectrometer for subsequent mass analysis.

3 It is yet another object of the invention to provide a method
4 and apparatus whereby a single robot is used for the automatic
5 preparation and introduction of samples into a mass spectrometer
6 for subsequent mass analysis.

7 It is still a further object of the invention to provide a
8 method and apparatus for the automatic preparation and introduction
9 of samples into a mass spectrometer from a plurality of
10 electrospray ionization (ESI) sprayers for subsequent mass
11 analysis.

12 Yet another aspect of the present invention is to provide a
13 capillary for use in an ion source having improved flexibility and
14 accessibility over prior art designs. A capillary according to the
15 invention consists of at least two sections joined together end to
16 end such that gas and sample material in the gas can be transmitted
17 through the capillary across a pressure differential. The
18 capillary is intended for use in an ion source wherein ions are
19 produced at an elevated pressure and transported by the capillary
20 into a vacuum region of the source.

21 Still another object of the invention is to allow for the
22 removal of one or more sections of the capillary (for cleaning or
23 replacement) without having to shut down the pumping system of the
24 instrument to which it is attached. These sections may be made of
25 different materials -- e.g., glass, metal, composite, etc. -- which

1 may be either electrically conducting or non-conducting. Also,
2 each section of the capillary according to the invention does not
3 have to be straight or rigid, rather, one or more of the sections
4 may be flexible such that it (or they) can bend in any direction.

5 Another object of the invention is to utilize a multiple part
6 capillary which offers improved flexibility in its geometric
7 orientation with respect to other devices in the ionization source
8 -- especially the ion production means. For example, the axis of
9 the bore or "channel" of the capillary at the capillary entrance
10 might be positioned at any angle with respect to the ion production
11 means. This angle, as discussed in Apfel U.S. Patent Nos.
12 5,495,108 and 5,750,988 can be important, for example, in the
13 separation of spray droplets from desolvated analyte ions. Also
14 according to the present invention, the entrance section of the
15 capillary might be modified or exchanged before or during
16 instrument operation to effect a change in the orientation of the
17 entrance with respect to the ion production means or other device.

18 This flexibility applies to the translational position of the
19 entrance of the capillary as well as its angular orientation. That
20 is, the position of the entrance of the capillary might be changed
21 before or during instrument operation by either modification or
22 exchange of the first section of the capillary. This allows for
23 the transmission of ions from a variety of locations either near or
24 removed from the immediate location of the source.

25 Still another object of the present invention is to utilize a

1 multipurpose multiple part capillary wherein the bore or "channel"
2 of one or more of the sections of the multiple part capillary may
3 comprise any useful geometry (i.e., straight, helical, wave-like,
4 etc.). For instance, it may be particularly useful to have an
5 inner channel of helical geometry. This will cause larger
6 particles (e.g., droplets from electrospray) to collide with the
7 walls of the capillary, while allowing smaller particles (e.g.,
8 fully desolvated electrosprayed ions) to pass through the
9 capillary. Note that the geometry of the bore may be, but is not
10 necessarily, related to the outer surface of the capillary. That
11 is, a capillary might have a cylindrically symmetric outer surface
12 but have an inner bore which is helical.

13 Yet another purpose of the present invention is to provide a
14 simple and efficient method and apparatus for integrating multiple
15 source assemblies. A complete ion source may include a multitude
16 of sub-assemblies. For example, an ion source might include an ion
17 production means sub-assembly and vacuum sub-assembly. The ion
18 production means sub-assembly might include a spray needle, its
19 holder, a translation stage, etc. The vacuum sub-assembly might
20 contain pumps, pumping restrictions, and ion optics for guiding
21 ions into the mass analyzer. In prior art ion sources and MS
22 instruments, the capillary would conventionally be integrated
23 entirely in one sub-assembly -- the vacuum sub-assembly. As a
24 result, significant effort is required in prior art systems to
25 align the ion production means sub-assembly -- specifically the

1 spray needle -- with the vacuum sub-assembly -- specifically the
2 capillary entrance. The multiple part capillary according to the
3 present invention eases the integration of such sub-assemblies by
4 including capillary sections in each of the sub-assembly. The sub-
5 assemblies are integrated by joining the capillary sections
6 together. Any necessary alignments are performed within a given
7 sub-assembly -- e.g. alignment of the spray needle with the first
8 section of capillary. This sub-assembly arrangement allows for the
9 automation of a MALDI-TOF mass spectrometer.

10 It is a further purpose of the present invention to provide
11 flexibility when using a particular mass spectrometer by providing
12 efficient use of a plurality of ionization sources. For example,
13 in combination with the ionization chamber described in co-pending
14 application serial no. 09/263,659, entitled IONIZATION CHAMBER FOR
15 ATMOSPHERIC PRESSURE IONIZATION MASS SPECTROMETRY, which is
16 incorporated herein by reference, the present invention provides
17 added flexibility for switching from one ionization source to
18 another or from one sample to another. Specifically, the capillary
19 according to the invention is capable of efficiently and accurately
20 being used with multiple electrospray sources. In addition, the
21 capillary according to the invention is useful in multiplexing.

22 Another purpose of the invention is to provide a multiple part
23 capillary which can be used with chromatographic sample preparation
24 (e.g., liquid chromatography, capillary electrophoresis, etc.).
25 The effluent from such a chromatographic column may be injected

1 directly or indirectly into one of the sprayers. A plurality of
2 such chromatographic columns may be used in conjunction with a
3 plurality of sprayers -- for example one sprayer per column. The
4 presence of analyte in the effluent of any given column might be
5 detected by any appropriate means, for example a UV detector. When
6 analyte is detected in this way, the sprayer associated with the
7 column in question is "turned on" so that while analyte is present
8 the sprayer is producing ions but otherwise the sprayer does not.
9 If analyte is present simultaneously at more than one sprayer, the
10 sprayers are multiplexed, as discussed above.

11 It is yet another purpose of the invention to allow a simple,
12 fast, efficient and reliable means of integrating a robot with
13 various ionization sources and techniques. The multiple part
14 capillary disclosed herein allows such a means for integrating a
15 robot with any of a variety of ionization sources, including
16 elevated pressure and atmospheric pressure sources. The design of
17 the multiple part capillary according to the present invention
18 provides added versatility to the use of ionization chambers as
19 well as to the use and performance of any new and existing
20 ionization methods.

21 Further, the present system allows for the removal of one or
22 more sections of the capillary (for cleaning or replacement)
23 without having to shut down the pumping system or the instrument to
24 which it is attached. The capillary according to the present
25 invention can, among other things, be made from different

1 materials, take on different sizes, shapes or forms, as well as
2 perform different functions. Furthermore, to provide a fully
3 automated system for the analysis of a variety of chemical species
4 efficiently and cost effectively.

5 Other objects, features, and characteristics of the present
6 invention, as well as the methods of operation and functions of the
7 related elements of the structure, and the combination of parts and
8 economies of manufacture, will become more apparent upon
9 consideration of the following detailed description with reference
10 to the accompanying drawings, all of which form a part of this
11 specification.

12 13 BRIEF DESCRIPTION OF THE DRAWINGS

14 A further understanding of the present invention can be
15 obtained by reference to a preferred embodiment set forth in the
16 illustrations of the accompanying drawings. Although the
17 illustrated embodiment is merely exemplary of systems for carrying
18 out the present invention, both the organization and method of
19 operation of the invention, in general, together with further
20 objectives and advantages thereof, may be more easily understood by
21 reference to the drawings and the following description. The
22 drawings are not intended to limit the scope of this invention,
23 which is set forth with particularity in the claims as appended or
24 as subsequently amended, but merely to clarify and exemplify the
25 invention.

1 For a more complete understanding of the present invention,
2 reference is now made to the following drawings in which:

3 FIG. 1 shows a partial cut-away cross-sectional view of a
4 prior art capillary comprising a unitary glass tube having a
5 cylindrical outer surface and internal bore;

6 FIG. 2 shows a partial cut-away cross sectional view of
7 another prior art capillary comprising a concentric outer capillary
8 sleeve and inner capillary tube;

9 FIG. 3 shows a prior art spray chamber of a prior art
10 electrospray ionization source wherein the channel of the spray
11 needle is oriented orthogonal to the channel of the capillary;

12 FIG. 4 shows a preferred embodiment of a multiple part
13 capillary according to the present invention;

14 FIG. 5 shows an alternate embodiment of the multiple part
15 capillary, wherein the channel of the first section comprises a
16 helical structure;

17 FIG. 6 shows an ESI sprayer needle oriented at an angle θ with
18 respect to the inlet to the channel and an angle α with respect to
19 the body of an embodiment of the multiple part capillary according
20 to the present invention;

21 FIG. 7 shows an embodiment of the multiple part capillary
22 according to the present invention as used with an ESI ionization
23 source;

24 FIG. 8 shows a multiple part capillary according to the
25 present invention as a means for integrating two source sub-

1 assemblies;

2 FIG. 9 shows the multiple part capillary according to the
3 present invention as a means for integrating a sample preparation
4 robot with an API source for mass spectrometry;

5 FIG. 10 shows an embodiment of the multiple part capillary
6 according to the present invention as a means for integrating a
7 sample preparation robot with an elevated pressure MALDI source for
8 mass spectrometry; and

9 FIG. 11 shows a close-up view of the use of the multiple part
10 capillary with a MALDI probe in accordance with the present
11 invention.

12
13 DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

14 As required, a detailed illustrative embodiment of the
15 present invention is disclosed herein. However, techniques,
16 systems and operating structures in accordance with the present
17 invention may be embodied in a wide variety of sizes, shaped,
18 forms and modes, some of which may be quite different from those
19 in the disclosed embodiment. Consequently, the specific
20 structural and functional details disclosed herein are merely
21 representative, yet in that regard, they are deemed to afford the
22 best embodiment for purposes of disclosure and to provide a basis
23 for the claims herein which define the scope of the present
24 invention.

25 The following presents a detailed description of a preferred

embodiment of the present invention, as well as some alternate embodiments of the invention. As discussed above, the present invention relates generally to the mass spectroscopic analysis of chemical samples and more particularly to mass spectrometry. Specifically, an apparatus and method are described for transport of ions to the mass spectrometer. Reference is herein made to the figures, wherein the numerals representing particular parts are consistently used throughout the figures and accompanying discussion.

With reference first to FIG. 4, shown is multiple part capillary 35 according to a preferred embodiment of the present invention. As depicted in FIG. 4, multiple part capillary 35 comprises: first section 28 having capillary inlet end 26 and first channel 27; union 29 having o-ring 31; second section 33 having second channel 32 and capillary outlet end 34; and metal coatings 30A and 30B. According to the preferred embodiment, first section 28 is connected to second section 33 by union 29. In the preferred embodiment, union 29 is substantially cylindrical having two coaxial bores, 60 and 61, and through hole 62 of the same diameter as channels 26 and 32. In the preferred embodiment, section 28 and union 29 are composed of metal - e.g. stainless steel. The inner diameter of bore 60 and the outer diameter of section 28 are chosen to achieve a "press fit" when section 28 is inserted into bore 60. Because the press fit is designed to be tight, union 29 is thereby strongly affixed to

1 section 28 and a gas seal is produced between union 29 and
2 section 28 at the surface of the bore. The inner diameter of
3 bore 61 is of slightly larger diameter than the outer diameter of
4 section 33 (including metal coating 30A) so as to produce a "slip
5 fit" between union 29 and section 33. A gas seal is established
6 between bore 61 and section 33 via o-ring 31. Electrical contact
7 between metal coating 30A, union 29, and section 28 via direct
8 physical contact between the three. Through hole 62 allows for
9 the transmission of gas from entrance end 26 through to exit end
10 34 of the capillary. Ideally, union 29 and sections 28 and 33
11 are formed in such a way as to eliminate any "dead volume"
12 between these components. To accomplish this, the ends of
13 sections 28 and 33 are formed to be flush with the inner surface
14 of union 29. Note that the body of section 33 - excluding metal
15 coatings 30A and 30B - is composed of glass in the preferred
16 embodiment. As a result, metal coating 30A - together with union
17 29 and section 28 - can be maintained at a different electrical
18 potential than metal coating 30B.

19 Alternatively, union 29, and sections 28 and 33 may be
20 composed of a variety of materials conducting or non-conducting;
21 the outer diameters of the sections may differ substantially from
22 one another; the inner diameters of the sections may differ
23 substantially from one another; either or both ends or any or all
24 sections may be covered with a metal or other coating; rather
25 than a coating, the ends or capillary sections may be covered

1 with a cap composed of metal or other material; the capillary may
2 be composed of more than two sections always with one fewer union
3 than sections; and the union may be any means for removably
4 securing the sections of capillary together and providing an
5 airtight seal between these sections.

6 Each end of union 29 could comprise a generally cylindrical
7 opening having an internal diameter slightly larger than the
8 external diameter of the end of the capillary section which is to
9 be inserted therein. In such an embodiment, a gas seal is made
10 with each capillary section via an o-ring similar to o-ring 31.
11 As a further alternative, one might use springs to accomplish
12 electrical contact between union 29 and sections 28 and 33. In
13 this case a conducting spring would be positioned in union 29
14 adjacent to o-ring 31.

15 Moreover, in a preferred embodiment of the capillary
16 according to the invention, the length of first section 28 is
17 less than (even substantially less than) the length of second
18 section 33. More specifically, the dimensions of first section
19 28 and second section 33 are such that within a range of desired
20 pressure differentials across capillary 35, a gas flow rate
21 within a desired range will be achieved. For example, the length
22 of second section 33 and the internal diameter of second channel
23 32 are such that the gas transport across second section 33 alone
24 (i.e., with first section 28 removed) at the desired pressure
25 differential will not overload the pumps which generate the

1 vacuum in the source chamber of the system. This allows the
2 removal (e.g., for cleaning or replacement) of first section 28
3 of capillary 35 without shutting down the pumping system of the
4 mass spectrometer.

5 While the prior art, as depicted in FIG. 2, attempts to
6 accomplish removal, without shutting down the vacuum, it is
7 difficult and cumbersome. As discussed previously, tools and
8 adhesives may be required to remove and replace the capillary.
9 The multiple part capillary according to the present invention
10 provides a much simpler method and apparatus for accomplishing
11 this result (i.e., without the use of adhesives, tools, etc.).

12 Turning next to FIG. 5, an alternate embodiment of capillary
13 35 is shown wherein capillary section 28 has a serpentine
14 internal channel 64. That is, the geometric structure of the
15 internal channel of the capillary section is sinusoidal. Of
16 course, other geometrical structures (i.e., helical, varying
17 diameter, non-uniform, etc.) may be used in accordance with the
18 invention. Having sinusoidal internal channel 64 causes larger
19 particles -- such as droplets from an electrospray -- to collide
20 with the walls of the channel and thereby not pass completely
21 through the capillary. On the other hand, smaller particles --
22 such as fully desolvated electrosprayed ions -- do not collide
23 with the walls and pass completely through the capillary. The
24 curved (or sinusoidal) geometry of channel 64 also increases the
25 length of the channel, which provides the advantage of permitting

1 a larger diameter channel. Such a larger diameter channel may be
2 advantageous in that it may provide greater acceptance of sampled
3 species (e.g., electrosprayed ions, etc.) at a given flow rate
4 and pressure differential. Alternatively, a sinusoidal -- or any
5 other geometry -- channel may be used in either first section 28
6 or second section 33, or both.

7 In accordance with the present invention, it is observed
8 that the introduction of ions from an ionization means into the
9 multiple part capillary of the invention may be accomplished at
10 any angle of incidence between the ionization means and the inlet
11 of the capillary. Referring now to FIG. 6, shown is an
12 embodiment of the multiple part capillary according to the
13 invention as used with an ESI sprayer 65 wherein axis 70 of
14 sprayer 65 is oriented at angle α 66 with respect to axis 69 of
15 the body of capillary 72. However, because channel 73 of
16 capillary section 74 is curved, angle θ 67 between sprayer axis
17 70 and axis 71 of channel entrance 68 can be substantially
18 different than angle α 66. The embodiment shown in FIG. 6
19 demonstrates that the capillary entrance angle α 66 may be any
20 angle from 0° and 180° . The specific angle selected is dependent
21 upon, among other things, the sample species being tested, the
22 ionization source used, etc. As discussed above, the
23 electrospray process results in the formation of charged droplets
24 and molecular ions. The presence of large droplets in the spray
25 can result in contamination of the capillary and generally poor

1 instrument performance. One way of limiting the influence of
2 large droplets on instrument performance is to spray away from
3 the capillary entrance. That is, the spray needle is oriented so
4 that it is not pointed directly at the capillary entrance. Large
5 droplets formed in a source with such a geometry will tend to
6 move along the axis of the spray needle and not enter the
7 capillary, whereas desolvated ions will be attracted to the
8 capillary entrance by the electrostatic field between the spray
9 needle and the capillary. Thus, in the embodiment of figure 6,
10 smaller angles α 66 and θ 67 will tend to reduce the fraction of
11 droplets that enter the capillary.

12 In any case, the sinusoidal geometry of channel 73 tends to
13 limit the contamination of capillary 72 due to large droplets
14 into section 74. Large droplets which enter the capillary will
15 tend to strike the walls of channel 73 and not pass through to
16 section 33. Section 74 can be removed from the system - by
17 pulling it off along axis 69 - and cleaned without necessarily
18 shutting the instrument or its vacuum system off.

19 Depicted in FIG. 7 is an ionization source which
20 incorporates the multiple part capillary of the invention where
21 the ion production means is an ESI sprayer device, shown as spray
22 needle 36 in spray chamber 40. During normal operation of a
23 preferred embodiment with an ESI source, sample solution is
24 formed into droplets at atmospheric pressure by spraying the
25 sample solution from spray needle 36 into spray chamber 40. The

1 spray is induced by the application of a high potential between
2 spray needle 36 and entrance 26 of first capillary section 28
3 within spray chamber 40. Sample droplets from the spray
4 evaporate while in spray chamber 40 thereby leaving behind an
5 ionized sample material (i.e., sample ions). These sample ions
6 are accelerated toward capillary inlet 26 of channel 27 by an
7 electric field generated between spray needle 36 and inlet 26 of
8 first section 28 of capillary 35. These ions are transported
9 through first channel 27 into and through second channel 32 to
10 capillary outlet 34. As described above with regard to FIG. 4,
11 first section 28 is joined to second section 33 in a sealed
12 manner by union 29. The flow of gas created by the pressure
13 differential between spray chamber 40 and first transfer region
14 45 further causes the ions to flow through the capillary channels
15 from the ionization source toward the mass analyzer.

16 Still referring to FIG. 7, first transfer region 45 is
17 formed by mounting flange 48 on source block 54 where a vacuum
18 tight seal is formed between flange 48 and source block 54 by o-
19 ring 58. Capillary 35 penetrates through a hole in flange 48
20 where another vacuum tight seal is maintained (i.e., between
21 flange 48 and capillary 35) by o-ring 56. A vacuum is then
22 generated and maintained in first transfer 45 by a pump (e.g., a
23 roughing pump, etc., not shown). The inner diameter and length
24 of capillary 35 and the pumping speed of the pump are selected to
25 provide as high a rate of gas flow through capillary 35 as

1 reasonably possible while maintaining a pressure of 1 mbar in the
2 first transfer region 45. A higher gas flow rate through
3 capillary 35 will result in more efficient transport of ions.

4 Next, as further shown in FIG. 7, first skimmer 51 is placed
5 adjacent to capillary exit 34 within first transfer region 45.
6 An electric potential between capillary outlet end 34 and first
7 skimmer 51 accelerates the sample ions toward first skimmer 51.
8 A fraction of the sample ions then pass through an opening in
9 first skimmer 51 and into second pumping region 43 where pre-
10 hexapole 49 is positioned to guide the sample ions from the first
11 skimmer 51 to second skimmer 52. Second pumping region 43 is
12 pumped to a lower pressure than first transfer region 45 by pump
13 53. Again, a fraction of the sample ions pass through an opening
14 in second skimmer 52 and into third pumping region 44, which is
15 pumped to a lower pressure than second pumping region 43 via pump
16 53.

17 Once in third pumping region 44, the sample ions are guided
18 from second skimmer 52 to exit electrodes 55 by hexapole 50.
19 While in hexapole 50 ions undergo collisions with a gas (i.e., a
20 collisional gas) and are thereby cooled to thermal velocities.
21 The ions then reach exit electrodes and are accelerated from the
22 ionization source into the mass analyzer for subsequent analysis.

23 Another application of the present invention is to provide a
24 simple and efficient method and apparatus for integrating two
25 source assemblies. As depicted in FIG. 8, a complete ion source

1 may include a multitude of sub-assemblies. For example, ion source
2 80 includes ion production means sub-assembly 81 and vacuum sub-
3 assembly 82. The ion production means sub-assembly 81 includes,
4 among other things, spray chamber 40 and spray needle 36. The
5 vacuum sub-assembly 82 includes among other things, pump 53 and ion
6 optical elements 49-52 and 55 having pumping restrictions at
7 elements 51 and 52 for guiding ions into the mass analyzer. In
8 prior art sources and instruments, the capillary would be
9 integrated entirely in one sub-assembly -- e.g., the vacuum sub-
10 assembly 82. As a result, significant effort is required in prior
11 art systems to align the ion production means sub-assembly 81
12 (specifically the spray needle) with the vacuum sub-assembly 82
13 (specifically the capillary entrance). The multiple part capillary
14 according to the present invention can be used to ease the
15 integration of such sub-assemblies by including capillary sections
16 in each of the sub-assembly.

17 In the embodiment of FIG. 8, capillary section 28 is an
18 integral component of ion production means sub-assembly 81 and
19 capillary section 33 is an integral component of vacuum sub-
20 assembly 82. Sub-assemblies 81 and 82 are integrated in part by
21 joining capillary sections 28 and 33 together via union 29. Any
22 necessary alignments are performed within a given sub-assembly
23 (e.g., alignment of spray needle 36 with entrance 26 of channel
24 27). In alternate embodiments, any variety of sub-assemblies might
25 be integrated, in part or in whole, by including capillary sections

1 in these sub-assemblies and subsequently joining these capillary
2 sections together as discussed with respect to FIG. 8. Further,
3 any number of sub-assemblies with any variety of functions might be
4 used. Such functions might include ion production, desolvation of
5 spray droplets via a heated capillary section, ion transfer to the
6 mass analyzer, etc. Clearly, any type of atmospheric pressure
7 ionization means, including ESI, API MALDI, atmospheric pressure
8 chemical ionization, nano electrospray, pneumatic assist
9 electrospray, etc., could be assembled into a source in this way.

10 The capillary according to the present invention might also
11 be used to transport ions from ionization means remote from the
12 mass spectrometer instrument. This is exemplified by the
13 embodiment shown in FIG. 9. Depicted in FIG. 9 is an embodiment
14 of the multiple part capillary according to the invention as used
15 for integrating a sample preparation robot with an Atmospheric
16 Pressure Ionization (API) source. Specifically, the system shown
17 comprises, among other things: robot 90; robot arm 91; sample
18 tray (not shown); source tray 92; sprayer 93; multiple part
19 capillary 98 comprising first section 28 having inlet 26, second
20 section 33 having outlet 34, and union 29; gas transport line 94;
21 source cover 95; vacuum sub-assembly 96; and mass analyzer 97.

22 Robots such as in the embodiment of FIG. 9 -- for example, a
23 Gilson 215 Liquid Handler Robot -- consist of a robot arm 91,
24 which may be used to manipulate samples, "trays" of samples,
25 sample containers, etc. Robot arm 91 may be used to move

1 samples, solutions, and reactants from one container (i.e.,
2 tubes, vials, or microtiter wells, etc.) to another. By mixing
3 analyte(s), solvent(s), and reactant(s) in a predefined way, the
4 robot may be used to prepare samples for subsequent analysis.

5 As depicted in FIG. 9, sample spray and ionization occurs
6 within robot 90 and only ions would be transported -- via
7 multiple part capillary 98 -- to mass analyzer 97. In the
8 particular embodiment shown, a specially prepared source tray 92
9 is used. Sample is obtained by robot 90 from a sample tray by
10 sucking solution into sprayer 93. Robot arm 91 using positioning
11 means then moves sprayer 93 from source tray 92 to a predefined
12 location near entrance 26 of capillary 98. Drying gas can be
13 transported into source tray from vacuum sub-assembly 96 via a
14 gas transport line 94. The drying gas may be used to assist the
15 evaporation of the droplets and passage of ions into capillary
16 98. Sprayer 93 is attached to robot arm 91 and set at ground
17 potential (of course, any ESI sprayer may be used (e.g.,
18 pneumatically assisted sprayers with or without pneumatic spray
19 lines, nanosprayer needles, high voltage sprayers, etc.)), while
20 inlet 26 to first section 28 of capillary 98 is set at a high
21 voltage via contact through union 29 and end cap 30A to a power
22 supply (not shown). This potential difference between sprayer 94
23 and first section 28 (in addition to pneumatic gas (if using a
24 pneumatic sprayer)) then induces the spray of the sample solution
25 and the production of analyte ions.

1 Once the ions enter inlet 26 of capillary 98 they are
2 carried with a drying gas into the vacuum system of the mass
3 spectrometer. This may comprise a plurality vacuum chambers 95,
4 96, 97 connected to differential pumps. Additionally, any number
5 of ion optical devices (i.e., electrostatic lenses, conventional
6 ion guides, etc.) may be used within the vacuum system to aid in
7 the transport of the ions to the mass analyzer. Once in the mass
8 analyzer, the sample ions are analyzed to produce a mass
9 spectrum. Some of the analyzers which may be used in such a
10 system include quadrupole, ICR, TOF, etc.

11 The capillary according to the present invention is also
12 useful in transporting ions from varying locations during
13 operation. Turning next to FIG. 10, shown is an embodiment of
14 the multiple part capillary according to the invention as a means
15 for integrating a sample preparation robot with an elevated
16 pressure MALDI source for use in mass spectrometry. The system
17 depicted in FIG. 10 comprises a laser 99, attenuator 100, fiber
18 optic 101, robot 90 having robot arm 91 for control and movement
19 of sample probe 102, MALDI sample tray 103, sample holder 104,
20 alternative embodiment of capillary 98 having first section 105,
21 second section 33 joined by union 29, ionization source cover 95,
22 vacuum sub-assembly 96, and mass analyzer 97.

23 The alternative embodiment of the multiple part capillary of
24 the invention as shown in FIG. 10 comprises a flexible first
25 section 105 such that its inlet end may be moved by robot arm 91

1 to various positions for acceptance of the MALDI samples to be
2 analyzed. As implied by FIG. 10, sample preparation and
3 ionization may both be performed by robot 90 such that only ions
4 would be transported through the multiple part capillary 98 to
5 vacuum sub-assembly 96 and ultimately to mass analyzer 97.
6 Specifically, robot arm has attached to its end sample probe 102,
7 and fiber optic 101 for directing the laser beam from laser 99
8 onto sample holder 104 to ionize samples thereon. Alternatively,
9 mirrors may be used to re-direct the laser beam from laser 99
10 onto sample holder 104 to ionize samples thereon. Yet another
11 alternative includes mounting laser 99 onto robot arm 91 or some
12 other robot arm, which would be able to direct the laser beam
13 onto the sample. This embodiment also allows for laser 99 to be
14 easily moved from one location to another with precision. The
15 ions formed by the laser beam hitting the samples on sample
16 holder 104 are then carried by the gas flow into and through
17 capillary 98 to the differential pumping region of vacuum sub-
18 assembly 96, where additional ion optics (not shown) are designed
19 to further transport the ions from outlet end of capillary 98 to
20 mass analyzer 97 for subsequent analysis. Any known ion optics
21 may be used, including but not limited to, electrostatic
22 electrodes, RF electrodes, optics of the type referred to in
23 Franzen et al. U.S. Patent No. 5,663,561 or Whitehouse et al.
24 U.S. Patent No. 5,652,427, etc.

25 As shown in FIG. 11, which depicts an embodiment of the

multiple part capillary for use with a MALDI probe, the multiple part capillary according to the invention provides a means for integrating a sample preparation robot with MALDI mass analysis. Shown in FIG. 11 are capillary 105, robot arm 91, receptacle 106, fiber optic 101, and sample plate 104 with raised conical formations 107 onto which samples (not shown) are deposited. Sample plate 104 and the conical formations form a unitary device composed of conducting material (e.g., stainless steel). In this alternate embodiment, capillary section 105 optionally comprises a specially shaped orifice which fits over cone-shaped sample holder formations 107 (one at a time) in such a way that gas flowing through capillary 98 readily captures the ions formed from the sample by laser desorption ionization. Therefore, the sample is desorbed directly into the gas flow, thereby resulting in a minimal loss of ions (i.e., for an efficient transfer of ions). Alternatively, chemical ionization may be performed in the capillary or in the vacuum for such efficient transfer of ions. Optionally, a potential may be applied between sample carrier 104 and capillary 78 section 105 to help draw ions into the channel of capillary 78 section 105. Also, fiber optic 101 might be adjusted via piezo electrics or other mechanics to direct the laser beam to any region of the specific cone-shaped sample of samples 107 to be ionized. Optionally, this redirecting of the laser beam may occur during the ionization process such that ultimately the entire sample is ionized. It is

1 noted that several laser "shots" may be needed to desorb the
2 entire sample.

3 While the present invention has been described with
4 reference to one or more preferred embodiments, such embodiments
5 are merely exemplary and are not intended to be limiting or
6 represent an exhaustive enumeration of all aspects of the
7 invention. The scope of the invention, therefore, shall be
8 defined solely by the following claims. Further, it will be
9 apparent to those of skill in the art that numerous changes may
10 be made in such details without departing from the spirit and the
11 principles of the invention. It should be appreciated that the
12 present invention is capable of being embodied in other forms
13 without departing from its essential characteristics.
14